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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,546	03/26/2001	Deborah J. Good	P 0279282	9489

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,546	GOOD ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,9 and 22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8, 9 and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 2-6-04 and "Change of Power Attorney" 1-6-04 have been entered. Claims 1 and 22 have been amended. Claims 1-6, 8, 9, and 22-27 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-6, 8, 9 and 22-27 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and is repeated for the reasons set forth in the preceding Official action mailed 8-1-03. Applicant's arguments filed 2-6-04 have been fully considered but they are not persuasive.

Applicants cite page 4 lines 16-25 and page 17 line 23 to page 18 line 2 of the specification and argue that the phenotype of PrP knockout mice was discussed and the difference of gene targeting between mice and cattle and the construction of a genomic library to facilitate gene targeting in cattle have been addressed (amendment, p. 4). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-1-03. As discussed in the preceding Official action mailed 8-1-03, the state of the art in the fields of transgenic animal at the time of the invention was unpredictable, the transgene expression and

resulting phenotype of such expression is not always accurately predictable. The individual gene of interest, coding or non-coding sequences present in the transgene construct, and the site of integration, etc., are important factors that governs the expression of a transgene. Similarly, it was unpredictable for generating transgenic animals harboring any disrupted gene. A major concern in generating a transgenic knockout animal is the potentially lethal effect of the targeted gene, such as early death of embryos and young animals. Variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" and "These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (Sigmund, 2000).

The claims encompass production of any transgenic ungulate, which include ruminants, horses, swine, camels, hippopotamus, tapirs, rhinoceros etc. Each of these ungulate species has different genetic background. Applicants also mention that there is a difference of gene targeting between mice and cattle. Thus, the resulting phenotype of a transgenic knockout ungulate having homologous deletion PrP gene was unpredictable at the time of the invention. The phenotype of transgenic mice lacking PrP gene expression can not predict the phenotype of any transgenic knockout ungulate having homologous deletion of PrP gene. The specification only teaches how to make the transgenic knockout ungulate but fails to produce any transgenic knockout ungulate founder animals or any line of transgenic knockout ungulate. Without making any transgenic knockout ungulate having homologous deletion of PrP gene, one skilled

in the art at the time of the invention would not know the resulting phenotype of said transgenic knockout ungulate and would not know how to use said transgenic knockout ungulate.

Applicants cite US Patent 6,147,276, incorporated by reference, and argue that said patent teaches a typical process by which transgenic and non-transgenic mammals may be prepared (amendment, p. 4). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-1-03 and the reasons set forth above. It should be noted that "incorporated by reference" of the US Patent 6,147,276 would introduce new matter into the present invention. The originally presented specification of the present invention does not incorporate the subject matter of the US Patent 6,147,276. Even if the subject matter of US Patent 6,147,276 is considered, the teaching of said patent still would not make the resulting phenotype of transgenic knockout ungulate predictable at the time of the invention for the reasons discussed above.

Applicants argue that claims 1 and 22 have been amended to recite the phenotype of the transgenic knockout ungulate and homologous deletion of the prion gene would naturally lead to animals that are less likely to incur prion-associated diseases (amendment, bridging p. 4-5). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-1-03 and the reasons set forth above. The phenotype of transgenic mice lacking PrP gene expression can not predict the phenotype of any transgenic knockout ungulate having homologous deletion of PrP gene. The specification only teaches how to make the transgenic knockout ungulate but fails to produce any transgenic knockout ungulate founder animals or any line of transgenic knockout ungulate. Without making any transgenic knockout ungulate having homologous deletion of PrP gene, one skilled in the art at the time of the invention would not

know the resulting phenotype of said transgenic knockout ungulate and would not know how to use said transgenic knockout ungulate.

Applicants argue that the specification teaches how to use the transgenic knockout ungulate for breeding or agricultural purposes, as an animal model, or for producing meat or milk. Applicants further argue that US Patent 5,945,577 encompasses production of transgenic ungulates (amendment, p. 5). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-1-03 and the reasons set forth above. The resulting phenotype of a transgenic knockout ungulate having homologous deletion PrP gene was unpredictable at the time of the invention. The specification only teaches how to make the transgenic knockout ungulate but fails to produce any transgenic knockout ungulate founder animals or any line of transgenic knockout ungulate. Without making any transgenic knockout ungulate having homologous deletion of PrP gene, one skilled in the art at the time of the invention would not know the resulting phenotype of said transgenic knockout ungulate and would not know how to use said transgenic knockout ungulate.

Applicants argue that the teaching of Kappell is related to making a transgenic animal which is irrelevant to making a transgenic knockout animal (amendment, p. 6). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-1-03. Although Kappell teaches factors that would influence the resulting phenotype of a transgenic animal, however, one of the methods of making transgenic knockout animal is by microinjection of DNA into pronucleii or target cells and those factors, such as individual gene of interest, coding or non-coding sequences present in the construct, and the site of integration, etc., could

still influence the resulting phenotype of the transgenic knockout animals. Therefore, the teaching of Kappell is relevant to the making of a transgenic knockout animal.

Applicants argue that the teaching of Wu reference does not represent the state of the art as of the filing of the present application and argue that nuclear transfer cloning result in successful homozygous targeted deletion in ungulates (Phelps et al., 2003) and disruption of the gene in mice did not lead to a lethal phenotype. Applicants further cite specification page 42 lines 7-14 and argue that applicants can produce transgenic animal by cloning at a reasonable high efficiency rate (amendment, p. 7). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-1-03 and the reasons set forth above. The teaching of Wu represents the problem encountered in making a transgenic knockout animal and is relevant to the state of the art of making knockout trasngenics at the time of the invention. The cited Phelps reference was published in 2003, which is three years after the effective filing date of the present invention, i,e, 3-24-00, therefore, the Phelps reference does not represent the state of the art of making transgenic knockout ungulate at the time of the present invention. The resulting phenotype of a transgenic knockout ungulate having homologous deletion PrP gene was unpredictable at the time of the invention. The phenotype of transgenic mice lacking PrP gene expression can not predict the phenotype of any transgenic knockout ungulate having homologous deletion of PrP gene. The specification only teaches how to make the transgenic knockout ungulate but fails to produce any transgenic knockout ungulate founder animals or any line of transgenic knockout ungulate. Without making any transgenic knockout ungulate having homologous deletion of PrP gene, one skilled in the art at the time of the invention would not

know the resulting phenotype of said transgenic knockout ungulate and would not know how to use said transgenic knockout ungulate.

Repeatable in the technique of using bovine somatic cell nuclear transfer does not make the resulting phenotype of a transgenic knockout ungulate having homologous deletion of PrP gene predictable. Applicants mention producing transgenic animals by cloning at a reasonable high efficiency, however, it is unclear what kind of transgenic animal is made, a transgenic animal expressing a trasngene or a transgenic knockout animal, and what trasngene is expressed or knockout, and what kind of method is used to make the transgenic animal. Further, applicants have observed that not all clonal lines, although originated from the same genome, will maintain the same level of efficiency. Therefore, as discussed above, the resulting phenotype of a transgenic knockout ungulate having homologous deletion PrP gene was unpredictable at the time of the invention.

Applicants argue that this application relates to a gene whose gene product is the cause of prion disease and the cited Sigmund reference would not reasonably be relevant to the present invention (amendment, p. 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-1-03 and the reasons set forth above.

Applicants argue that there is no known function of the nociceptin system in the cited Nishi reference and the knockout mice cited by Nishi do not correlate to the transgenic ungulate of the present invention where the PrP gene is known to be essential for prion disease (amendment, p. 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-1-03 and the reasons set forth above. Although the physiological roles of the nociceptin system have not been elucidated yet at the whole animal level, it does not mean

that the biological function of the nociceptin system is unknown. In fact, the results from several groups have suggested that the nociceptin system plays important roles in modulation of the nociceptive threshold, locamotor activity, immunological responses and neuronal development. Regardless of the biological function of the nociceptin system, Nishi shows that a transgenic mice lacking the nociceptin receptor does not result in significant differences in nociceptive threshold and locomotor activity as compared to control mice and further strengthen the unpredictability of the resulting phenotype of a transgenic knockout animal. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed. Therefore, claims 1-6, 8, 9 and 22-27 remain rejected under 35 U.S.C. 112 first paragraph.

Conclusion

No claim is allowed.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.